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(54) Topical Pharmaceutical Compositions

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Abstract of the Disclosure

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A skin penetration pharmaceutical composition incorporating a difficultly skin-penetrable pharmacologically active agent, wherein the composition is in the form of a microemulsion formed from skin compatible excipients.

TOPICAL PHARMACEUTICAL COMPOSITIONS

This invention relates to topical pharmaceutical compositions, particularly those containing pharmacologically active agents which only difficultly penetrate the skin horny layer.

The therapeutic efficiency of a topical pharmaceutical composition depends upon inter alia the availability of the pharmacologically active agent for absorption and the skin-penetrability of the active agent. Before any topically applied pharmacologically active agent can act at its site of action whether in the deeper dermal layers below the horny layer or elsewhere in the body it must penetrate the barrier of the horny layer of the skin (stratum corneum). The penetration of the stratum corneum is the rate-limiting step of the total percutaneous process and is accompanied by the creation of a reservoir of pharmacologically active agent, i.e. the deposition of pharmacologically active agent on and in the layer. In the rare case the pharmacologically active agent is normally liquid and penetrates the skin layer efficiently, e.g. isosorbide dinitrate or glyceryl trinitrate.Otherwise various methods must be employed to obtain sufficient penetration of the pharmacologically active agent through the horny layer, especially for active agents which are generally administered in solid form. Often the pharmacologically active agent is capable of penetrating the skin horny layer when applied to the skin in a conventional system such as a triglyceride or paraffin ointment, but has a penetration flux of less than about 10^{-9} Mol cm^{-2} hour^{-1}, e.g. 10^{-10} Mol cm^{-2} hour^{-1}. Such pharmacologically active agents are hereinafter referred to as difficultly skin-penetrable pharmacologically active agents.

One method to increase the penetration rate is to dissolve the ———— skin-penetrable pharmacologically active agent in a non-toxic solvent which is skin compatible e.g. that ——does not cause skin irritation over an extended period of time as indicated in standard tests using human skin or —— more sensitive guineapig skin. The solutions may be applied in the form of macroemulsions, i.e. opaque oil-in-water or water-in-oil systems formed from water and water immiscible organic solvents in the presence of an emulsifier.
Such systems suffer from disadvantages especially in the case of ———————— difficultly skin-penetratable pharmacologically active agents.

We have now found that skin penetration pharmaceutical compositions wherein the composition is in the form of a microemulsion have particularly advantageous properties in respect of difficultly skin-penetrable pharmacologically active agents.

A recent review on microemulsions is by M.Rosoff p.405 in Progress in Surface and Membrane Science 12, 1978 Academic Press. A microemulsion is generally recognised to be a coloured or colourless (oil-in-water or water-in-oil) emulsion wherein the diameter of the particles or droplets are less than about 1500 Angstrom units (150 nm) which is less than 1/4 of the wavelength of light. They do therefore not scatter visible light, the diameter of the particles or droplets arising from e.g. any micellar aggregate structure present being sufficiently small. The emulsion thus appears transparent when viewed by optical microscopic means. It may be isotropic or anisotropic. An anisotropic structure may however be observable using x-ray techniques. The particles in a microemulsion may be spherical but other structures are feasible, e.g. liquid crystals with lamellar, hexagonal or isotropic symmetries.

Usually microemulsions are produced from an emulsifier (a surfactant) and a co-emulsifier (i.e. a co-surfactant, polar additive, co-solubilizer) which lowers the interfacial tension between the oil-in-water phases to a very small amount (typically less than 1 dyne/cm). The microemulsions often form practically spontaneously and represent a single thermodynamically stable phase. In contrast, macroemulsions are thermodynamically unstable two phase systems, and in their formation energy supply in the form of heating or rapid agitation is required.

Microemulsions are well known in other fields,e.g.cosmetic preparations,floor polishes,paints and foods.However,the formulation of microemulsions is to a certain extent largely empirical (see for example p.34-56 in Microemulsions Theory and Practice,Ed.L.Prince,1977) and up to now no skin penetration pharmaceutical composition for the systemic administration of a difficultly skin-penetrable pharmacologically active agent has been produced from skin compatible excipients.

J. Ziegenmeyer and C.Fuhrer in Acta Pharmaceutica Technologica 1980, 26 (4) p.273-275 have disclosed a microemulsion pharmaceutical composition containing 1% tetracycline. hydrochloride and decanol.However,the composition is not capable of producing a systemic therapeutic effect amount of tetracycline as the tetracycline concentration in the pharmaceutical composition is too low. More importantly decanol is not skin compatible. For example in sensitive animal skin irritation tests, moderate irritation of guinea pig skin and severe irritation of the rabbit skin has been found, see for example Industrial Hygiene and Toxicology Second Revised Edition, Editor F.Patty,Vol.II,(1962),p.1467, Interscience Publishers, John Wiley, New York and London. In less sensitive tests using human skin exposed to decanol over a 24 hour period, significant irritation has been observed, see - for example p.753 W.Kästner, J.Soc. Cosmet.Chemists (1974) 28, 741-754. Additionally the specific hydrocarbon solvents suggested are not applicable for man.

We have found that microemulsions may be made containing pharmacologically active agents and skin compatible excipients which show particularly advantageous penetration properties producing a penetration flux sufficient to produce a therapeutic effect in the deeper dermal layers or through the systemic circulation as indicated in trials mentioned hereinafter.

In one aspect the present invention provides a skin penetration pharmaceutical composition incorporating a ______ skin-penetrable pharmacologically active agent, wherein the composition is in the form of an microemulsion formed from skin compatible excipients.

In another aspect the present invention provides a method of enhancing the penetration of a ______ skin-penetrable pharmacologically active agent through the skin which comprises applying the active agent to the skin in the form of a microemulsion consisting of skin compatible excipients.

In a further aspect the present invention provides the use of a microemulsion consisting of skin compatible excipients to administer percutaneously ______ a skin-penetrable pharmacologically active agent.

In yet a further aspect the present invention provides a process for the production of a skin-penetrable pharmaceutical composition which comprises forming a microemulsion from water and a ______ skin-penetrable pharmacologically active agent and skin compatible excipients capable of functioning as a water-immiscible organic solvent, an emulsifier, and a co-emulsifier.

The microemulsions may be produced in conventional manner for the preparation of topical pharmaceutical compositions. The skin compatible pharmacologically active agent, water-immiscible organic solvent, water,emulsifier and co-emulsifier may be mixed,conveniently at a maximum of 100°C,e.g. from about 60° to about 95°C and the mixture is cooled. It is not important that a microemulsion be formed above 32°C.

If a microemulsion is formed above 32°C then the phase inversions should preferably be reversible. Indeed it is quite common that a milky macroemulsion may be formed at high temperatures which on cooling passes through one or more cloudy transitional phases alternately with microemulsion phases.
Desirably a microemulsion is produced throughout the temperature range of from about 20°C to about 32°C, preferably from about 15°C to about 35°C.

The water-immiscible organic solvent may be for example a hydrocarbon or lipid.

An emulsifier is present to form an oil-in-water or water-in-oil emulsion wherein the oil is the water-immiscible organic solvent. The co-emulsifier contributes to the formation and the stability of the microemulsion.

The chemical structure or chainlength of the co-emulsifier is a governing factor in controlling the size of the droplets or particles in the emulsions and should match the structure or chainlength of the hydrocarbon part of the emulsifier. The co-emulsifier should be compatible with the water-immiscible organic solvent forming the lipophilic phase. The organic solvent emulsifier and co-emulsifier should also be compatible with the pharmacologically active agent.

Naturally it is possible that the same excipient acts as a water-immiscible organic solvent and simultaneously as a co-emulsifier. Conveniently different excipients are used as organic solvent and co-emulsifier, however.

The microemulsions may be colourless or coloured, e.g. yellow.

A suitable combination of an emulsifier with a co-emulsifier may be, for example, a water-soluble non-ionic emulsifier and a fatty alcohol of a suitable chain length. Another suitable combination may be a mixture of water-soluble and water-insoluble non-ionic tensides. Conveniently at least two of the water-immiscible oganic solvent, co-emulsifier and emulsifier has a chain length moiety of 12 to 20 carbon atoms.

For any particular skin compatible pharmacologically active agent, water-immiscible organic solvent,water,emulsifier, and co-emulsifier system the relative amount of excipients can be varied and full phase equilibria diagrams may be drawn. It is sometimes more convenient merely to obtain a microemulsion at any temperature, even above room temperature, from one set of excipients in order to show they are compatible and then vary the amounts slightly to produce a suitable microemulsion at room temperature. As a very rough guide the microemulsion may contain:-

a) 0.01 to 15% of skin compatible skin-penetrable pharmacologically active agent,

b) 5 to 30%,e.g. 10 to 30%, of skin compatible water-immiscible organic solvent,

c) 10 to 30% of skin compatible emulsifier,

d) 4 to 30% of skin compatible co-emulsifier, and

e) 15 to 55% water.

Where the same compound may act as,e.g.both water-immiscible organic solvent and co-emulsifier,and in particular when another co-emulsifier or organic solvent is omitted then a part of the concentration of the compound (together with any other water-immiscible solvent present) may be reckoned as water-immiscible solvent and a part (together with any other co-emulsifier present) as co-emulsifier.

Where the same excipient acts as both water-immiscible organic solvent and co-emulsifier and there is no co-emulsifier or organic solvent present then this excipient may be present from 9 to 60% of the composition.

The microemulsions of the invention may be in the form of liquids or preferably in the form of gels, which are semi-viscous, containing less water. Some microgels may have appropriate viscoelastic properties to form swinging gels.

In respect of any of the excipients mentioned hereinafter any aliphatic carboxylic acid may be straight-chain or branched and saturated or unsaturated, preferably with one or two double bonds. Any aliphatic alcohol is a univalent alcohol unless otherwise mentioned, and is preferably a secondary or especially a primary alcohol. They are branched or preferably straight-chain and are unsaturated with preferably one or two double bonds or especially saturated. Any glyceryl ether or ester is primarily etherified or esterified at one or both of the terminal glyceryl hydroxy groups

Suitable skin compatible excipients may be the following:-

1) an ester of an aliphatic (C_{3-18}) alcohol with an aliphatic (C_{10-22}) carboxylic acid, or
2) a hydrocarbon having a straight carbon (C_{12-32}) chain substituted by from 6 to 16 methyl groups and having up to 6 double bonds,
may be suitable water-immiscible organic solvents.

Examples of class 1) include isopropyl laurate, hexyl laurate and decyl laurate, isopropyl myristate and lauryl myristate.

Particularly suitable examples are isopropyl laurate, hexyl laurate and isopropyl myristate, especially hexyl laurate.

Examples of class 2) include terpenes such as polymethylbutanes and polymethylbutenes, e.g. 2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22 tetracosahexaene, also known as squalene ($C_{30}H_{50}$) and the perhydro analogue, squalane. A particularly suitable example is squalane.

Skin compatible excipients chosen from

3) a mono-ester of ethylene glycol or propylene glycol with an aliphatic (C_{6-22}) carboxylic acid,
4) an ester of an aliphatic (C_{12-22}) alcohol with lactic acid, or
5) a mono-or diester of glycerol with an aliphatic (C_{6-22}) carboxylic acid,
may be suitable for use as water-immiscible organic solvents and/or co-emulsifiers.

When a excipient of any of classes 3),4) or 5) is present as an organic solvent, then the same or different excipient may be present as a co-emulsifier.

Examples of class 3) include propylene glycol mono-laurate and propylene glycol monomyristate and preferably propylene glycol monolaurate. An example of class 4) is myristyl or preferably lauryl lactate.An example of class 5) is glyceryl caprolate.

Any skin compatible excipients chosen from

6) an ester of a poly(27)ethylene —— glycol glycerol ether having at least one free hydroxyl group and an aliphatic (C_{6-22}) carboxylic acid,
may be suitable for use as water-immiscible solvents or co-emulsifiers.
Some of this class may be water-miscible when for example the polyethylene glycol moiety has a low molecular weight, and so will not be suitable as organic solvents,but they may be suitable co-emulsifiers.An example is poly(7)ethylene glycol glyceryl cocoate.
If the excipient is a transesterification product of a vegetable oil triglyceride and a polyethylene glycol of molecular weight 200 to 400,e.g. as described in USP 3,288,824,

then the products may be water-immiscible and suitable for use as an water-immiscible organic solvent.

Skin compatible excipients chosen from

7) aliphatic (C_{12-22}) alcohol, or

8) an ester of having at least one hydroxyl group of a poly-(2-10)-glycerol with an aliphatic (C_{6-22}) carboxylic acid,

may be also suitable co-emulsifiers.

Examples of class 7) include dodecanol, tetradecanol, oleylalcohol, 2-hexyldecanol, and 2-octyl-decanol. Particularly suitable examples include tetradecanol and especially dodecanol.
Preferably the alcohol is liquid at 32°C.

Skin compatible excipients chosen from

9) a mono-ether of a poly-ethylene-glycol with an aliphatic (C_{12-18}) alcohol, having an HLB value of from 10 to 18, or

10) an ester of an aliphatic (C_{6-22}) carboxylic acid with
a) a polyethylene glycol
b) a saccharose
c) a sorbitan or
d) a poly-ethylene glycol sorbitan ether,

the ester having an HLB value of from 10 to 18, may be suitable emulsifiers.

Preferably the emulsifiers have an HLB value of from 12 to 15 (HLB values are an indication of the hydrophilic-lipophilic balance in an emulsifier and have been discussed extensively in the literature, see for example Pharm.Act.Helv. (1969) 44,9 and H.P.Fiedler, Lexicon der Hilfsstoffe für Pharmazie, Kosmetic und angrenzende Gebiete, 2nd Edition, 1981, Editio Cantor AG, BRD).

A preferred example of class 9) is commercially available polyoxyethylene-(10)-oleyl ether.

Preferably the microemulsions are made up from excipients from class 1) and 2) as water-immiscible organic solvents; especially class 1); class 7) as co-emulsifier and class 9) as emulsifier.

The exact choice of organic solvent, emulsifier and co-emulsifier will depend on inter alia the pharmacologically active agent used.

The pharmacologically active agent may be any compound ________________ which can , penetrate the skin horny layer, e.g. of molecular weight up to about 3,000, although higher molecular weight compounds may possibly be used.

In general the molecular weight of the pharmacologically active agent is conveniently below 1000. Conveniently the active agent has a good hydrophilic/lipophilic balance. The molecule of the active agent for example may be conveniently structurally compact, may contain aromatic groups and —— conveniently does not contain many reactive groups such as hydroxyl groups.

The microemulsions of the invention are capable of containing very high amounts of active agents, e.g. from 5% up to 15% or even up to 20% of the total weight. When a systemic action is desired, the pharmacologically active agent should be sufficiently active to be able to produce a systemic therapeutic effect when penetration the skin at rates of the order of 10^{-8} Mole cm^{-2} $hour^{-1}$. When a local action in the deeper dermal layer is required, then a skin penetration flux of 10^{-9} Mole cm^{-2} $hour^{-1}$ may be sufficient. Suitable agents may be for example those with an, e.g. oral, daily dose of about 0.1 to about 20 mg, preferably up to 1 mg.

The microemulsions of the invention may be indicated for the systemic administration of any active agent. They may be conveniently used for prophylactic agents and myotonolytics. The microemulsions of the invention may be indicated for the administration of pharmacologically active agents which act under the horny layer, e.g. anti-acne agents and anti-fungal agents.

Examples of active agents include (E)-N-methyl-6,6-dimethyl-N-(naphthylmethyl)hept-2-en-4-inyl-1-amine, proquazone, (E)-N-methyl-N-(1-naphthylmethyl)-3-phenyl-propen-2-yl-amine (hereinafter naftifin), 4-(1-methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta-[1,2-b]thiophen-10(9H)-one (hereinafter ketotifen), 4-(1-methyl-4-piperidylidene)-9,10-dihydro-4H-benzo-(4,5)-cyclohepta(1,2-b)-thiophene (hereinafter pizotifen), griseofulvin, fluocinolone acetonide, Triamcinolone acetonide, and 14-O-[5-(2-amino-1,3,4-triazolyl)thioacetyl]-dihydro-mutiline, and preferably (+)-1-methyl-2-[2-(α-methyl-p-chlorodiphenyl-methoxy)-ethyl]-pyrrolidine (hereinafter clemastine) and especially 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole (hereinafter tizanidine).

In respect of clemastine a microemulsion preferably contains any of the following concentrations:-

5 to 15% of clemastine.
5 to 30% of an water-immiscible organic solvent.
15 to 25% of an emulsifier.
5 to 25% of a co-emulsifier.
10 to 45% of water.

More preferably a microemulsion contains any of the following concentrations:-

7.5 to 12.5% of clemastine.
7.5 to 28.5% of water-immiscible organic solvent.
19.5 to 22% of an emulsifier.
7.5 to 22.5% of a co-emulsifier.
13 to 42% of water

More especially a clemastine microemulsion contains any of the following concentrations:-

8 to 12% of clemastine.

8 to 27% of water-immiscible organic solvent.

20 to 21% of an emulsifier.

8 to 21% of a co-emulsifier.

15 to 40% of water.

The excipients are preferably chosen from class (1) as defined above, as organic solvent. The excipients of class (3) as defined above may be present as organic solvent or co-emulsifier, especially propylene glycol mono-laurate. The co-emulsifier alternatively is an excipient of class (6) as defined above especially poly(7)ethylene glycol glyceryl cocoate, or propylene glycol myristate. The preferred emulsifier is chosen from class (9) as defined above, especially polyoxyethylene (10) oleyl ether e.g. having an HLB value of about 12 to 13.

With clemastine microgels containing high concentrations of clemastine can be produced whereas it is very difficult to produce stable macroemulsions containing such high clemastine concentrations.

In the respect of tizanidine a microemulsion preferably contains any of the following concentrations:-

6 to 10% of tizanidine.

15 to 25% of water-immiscible organic solvent.

15 to 25% of an emulsifier.

5 to 10% of a co-emulsifier.

30 to 35% of water.

Preferably the microemulsion contains any of the following concentrations:-
7.5 to 8.5% of tizanidine.
19.5 to 21.5% of water-immiscible organic solvent.
19 to 22% of an emulsifier.
5.5 to 21.5% of a co-emulsifier.
32 to 42% of water.

More particularly the microemulsion contains any of the following concentrations:-
8 to 8.4% of tizanidine.
20 to 21% of water-immiscible organic solvent.
20 to 21% of an emulsifier.
6.2 to 8.4% of a co-emulsifier.
33 to 42% of water.

Naturally the choice of water-immiscible organic solvent, emulsifier and co-emulsifier for a microemulsion system will vary from pharmacologically active agent to pharmacologically active agent, and in some cases a particular excipient may be suitable in one system as e.g. an water-immiscible organic solvent and in another system as an e.g. co-emulsifier.

The pH of the pharmaceutical composition may be adjusted to a skin compatible pH with appropriate acids or bases, preferably weak acids or bases e.g. lactic or acetic acid. It is preferred that the pharmacologically active agent is at least partially present in free form, e.g. free base form/as the skin penetration may be increased. Conveniently the pH of the microemulsions are weakly acidic.

Other skin compatible agents may be present, e.g. water-miscible solvents such as propylene glycol, and ethanol

and isopropanol, or water soluble film-forming agents used in cosmetic preparations, e.g. partially hydrolysed collagen yielding medium-weight polypeptides, to diminish solvent evaporation after rubbing on the skin.

Naturally the microemulsion should be composed of components that are skin compatible. The components should be non-toxic, non-allergic and well-tolerated by the skin tissue. Such components can be chosen by standard acute and chronic tests.
The tests may be effected on human skin or with more sensitive animal skin, e.g. guinea-pig skin.

The microemulsions of the invention are indicated for use in the percutaneous administration of pharmacologically active agents because of the skin penetration enhancing effects, and the capacity of the skin microemulsions to contain large amounts of pharmacologically active agents.
The skin-penetration enhancing effect may be observed in standard in vitro and in vivo tests for example using human skin.

One in vitro test is the well-known diffusion test which may be effected according to the principles described by H.Schaeffer et al in Adv.Pharmacol.Ther.[Proc.7th Int. Congr .Pharmacol.] 9,223-235 (1978) ed by Y.Cohen, Pergamon,Oxford (1979); H.Schaeffer et al pp.80-94 in Current Problems in Dermatology 7,Ed. G.A.Simon et al., Karger,Basel (1978);and J.M.Franz et al,Arch. Dermatol. Res.(1981), 271:275-282,using isolated human skin.

Microemulsions with the pharmacologically active agent in radio-active labelled form are applied to isolated pieces of unbroken human abdominal skin of about 2 square centimetres in area, at an amount of about 5 to about 10 mg of microemulsion per square centimetres. The skin is maintained at 32°C as a barrier between an upper chamber and physiological saline placed in a lower chamber. After 100,300 and 1000 minutes at 32°C the skin is fixed on a stopper. The residue is removed from the skin surface by a cotton swab and the radioactivity measured. The horny layer is removed by stripping and the radioactivity is determined in each individual stripping. The remaining skin is congealed and sliced into sections of about 20-40 μ with a microtome.. The radioactivity in the various slices is determined. The radioactivity in aquous saline in contact with the underside of the skin is also measured.

Since the penetration of the pharmacologically active agent through the horny layer represents in general the rate limiting step, the amount of pharmacologically active agent that has passed the horny layer is relevant to the systemic activity. This fraction of pharmacologically active agent contained in the different dermal layers, i.e. epidermis, upper corium (ca 800 microns thick), lower corium (ca 1000 microns thick) and sub-cutis (ca 1500 microns thick), would in vivo be removed by the capillary system into the blood stream and hence into the general circulation.

For convenience the fraction of the pharmacologically active agent that has penetrated the horny layer after 16 hours and is present in the deeper dermal layers is measured to give a mean percutaneous penetration flux (F) on the basis of a number of trials (n) as well as a percutaneous resorption quota in % of the applied dose (RQ).

Results obtained are as follows:-

Example* No	F(0-16 hours) X 10^8 Mol cm^{-2} $hour^{-1}$	n	RQ (%)
1	2.6 ± 0.5	8	24%
3	1.4 ± 0.3	20	14%
4	ca 1.6	4	13%
5	ca 2.6	4	21%
13	1.3 ± 0.01	12	12%
14	1.7 ± 0.7	8	12%
17	ca 1.2	4	15%
18	ca 1.7	4	25%
20	ca 1.3	4	12%
25	1.6 ± 0.6	8	13%

* The examples are listed hereinafter.

In vivo trials may be effected,e.g. including a comparative oral and percutaneous administration of the pharmacologically active agent in a cross-over study in a healthy subject.

In one study 480 mg of a microemulsion in the form of a gel as described in Example 1 containing 40 mg of active agent,tizanidine, was applied behind the ear, or a tablet containing 4 mg tizanidine, was administered orally.

The urine was collected over 72 hours and the amount of unchanged active agent and corresponding two metabolites were measured separately.

The results obtained were as follows:-

Period after administration	unchanged drug after oral administration [μg/hr]	unchanged drug after percutaneous administration [μg/hr]
0-2	3.08	0.03
2-4	1.61	1.01
4-6	0.53	1.81
6-8	0.24	1.33
8-12	0.04	3.36
12-24	---	4.16
24-36	---	2.54
36-48	---	1.57
48-60	---	1.10
60-72	---	1.07

Cumulative % absorption	oral	percutaneous
of tizanidine	0.28 %	0.37 %
of Metabolite A	2.5 %	0.4 %
of Metabolite B	1.1 %	0.16 %

The above results confirm the significant percutaneous absorption obtained in the in vitro tests, and indicate a sustained- release effect. Additionally the relatively lower amount of metabolite found indicates a significantly lower first pass effect.

100 mg of the clemastine composition of Example 3 (containing 10 mg clemastine) is applied behind the ear of 2 or 3 subjects (age 18 to 38 years) corresponding to an amount of active agent of 10 mg of clemastine. The amount of active agent in the urine is determined according to the principles of R.Tham.Arzneim.Forsch. (1978) 28 (1), 1017.

Period after administration	active agent in urine[µg/hr]	Subjects
hours		
0-6	--	3
6-8	0.486 ± 0.164	3
8-12	0.890 ± 0.384	3
12-24	1.042 ± 0.621	3
24-36	1.101 ± 0.422	3
36-48	1.469 ± 0.455	3
48-60	0.504 ± 0.211	2
60-72	0.231 ± 0.05	2

% Cumulative elimination of unchanged drug 0.664 ± 0.183

In comparison 2 mg of clemastine given orally over 72 hours yield 7.10% ± 0.46% of the unchanged drug in the urine.

The results show an excellent effect with the maximum concentration in the urine occurring 36 hours after administration and a resorption quota of about 10% of the clemastine topically administered.

As indicated by the above results the microemulsions of the present invention may produce systemic action of the pharmacologically active agent. In particular we have surprisingly found that topical administration of tizanidine is feasible.
The present invention accordingly provides a topical pharmaceutical composition containing tizanidine as active agent. In another aspect the present invention provides a method of topically administering tizanidine to a subject in need of such treatment.

The penetration rate observed may thus be at least in the order of 1 to 3 x 10^{-8} Mole cm^{-2} hour $^{-1}$ to produce a systemic action and in the order of about 1 x 10^{-9} Mole cm^{-2} $hour^{-1}$ to produce local action in the deeper dermal layers and the concentration of pharmacologically active agent in the microemulsion may be chosen accordingly.

The amount of pharmacologically active agent to be administered in the microemulsions of the present invention will depend inter alia on the penetration rate of the pharmacologically active agent observed in the in vitro or in vivo tests, the potency of the active agent, the size of the skin area treated with the microemulsion, the part of the body treated and the duration of action required.
In general a suitable daily dose is about from 5 to 20 times the dose effective in oral or topical administration, and the dose may be increased if longer duration than 1 day is required.
In general a suitable application area is from about 1 to about 4 square centimeters. The microemulsions of the invention may be applied in conventional manner.

In the case of liquid preparations,the microemulsion can be applied for example from a plexiglass container in contact with e.g. the upper arm,or from a plaster soaked with the microemulsion placed e.g.behind the ear.In the case of semi-solid microgels these may be rubbed in the skin.

For example in the case of tizanidine and clemastine a suitable single dose is from 10 to 50 mg,and this may last for up to 3 days.

The microemulsions of the invention may be used for the same indication that other forms of the pharmaceutically active agents are used for,e.g. clemastine as an anti-histamine agent,and tizanidine as myotonolytic,anti-depressant or minor tranquillizer.

The microemulsions of the invention may enhance the penetration of the pharmacologically active agent which is accumulated in the horny layer of the epidermis. A depot effect may then result whereupon the pharmacologically active agent slowly passes into the systemic circulation without inactivation by the liver resulting in a long-lasting concentration of active agent in the blood (retard effect). The blood concentration achieved by percutaneous delivery may be characterized by the absence of an initial drug concentration blood peak in contrast to oral administration.Side effects may be minimized. Additionally the accumulated pharmacologically active agent in the horny layer may provide a local effect if the pharmacologically active agent is locally active.

The microemulsions of the invention may in general possess significant other advantages over macroemulsions.For example they may in general be thermodynamically stable,and show little or no coalescene. In general the microemulsions of the invention have good spreading properties on the skin surface.They don't in general stick to the surface of the skin but may be easily rubbed in.They may leave little greasy feeling behind and may be washed off with water if desired. The skin may not be significantly dehydrated as the single water-containing phase may be easily available to the skin.

The following Examples illustrate the invention:-

Polyoxyethylene-(10)-oleyl ether is for example either BRIJ® 97 having an HLB value of 12.4 available from Atlas, Essen, W.Germany, or VOLPO® 10 having an HLB value of 12.4 available from Croda, Humberside, UK.

Polyethylene glycol glycerol fatty acid ester is for example brand Labrafil® M 1944 S available from Gatte-fosse, Boulogne, France.

Hexyllaurate is for example brand CETIOL® A, available from Henkel, Düsseldorf..

Polyethyleneglycol-(7)-glyceryl cocoate is for example brand CETIOL® HE available from Henkel,

Lactic acid is a 90% pure aqueous solution

Colladerm® 350 is a zinc salt of highly purified collagen-derived cosmetic medium molecular weight polypeptide available from Stepan Chemical Company, Northfield, Ill, USA.

Lauryl lactate is for example brand Ceraphyl® 31, and myristyl lactate is for example brand Ceraphyl® 50 from Van Dyk, Belleville, N.J., USA.

Further details on these products can be obtained from Fiedler H.P.Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Chemie, 2nd Edition, Editor Cantor.

EXAMPLE ONE: Tizanidine microgel

500 g of a mixture having the following composition :-

	Per cent	
Tizanidine	8.2	
Isopropyl laurate	20.5	
Polyoxyethylene (10) oleyl ether	20.5	(Brij 97)
Dodecanol	6.5	
Water	41.0	
Lactic acid	3.3	

are made and warmed by a water bath at about 90°C. The mixture is allowed to cool to room temperature by cooling the water 1°C per minute:

As the mixture is cooled various different phases are observed as follows:-

Phase	Temperature
Milky macro-emulsion	92-72°C
Transitional light cloudy phase	72-70°C
Microemulsion transparent phase	70-66°C
Transitional light cloudy phase	66-63°C
Microemulsion transparent phase	63-51°C
Transitional light cloudy phase	51-46°C
Microemulsion transparent phase	46°-room temperature

The cooled gel is filled into metal tubes.

Example	Active agent ingredient		Org.Solvent		Co-Emulsifier		Emulsifier		dist. water	Additional excipients	
	No.	%	a		b	%	c	%			%
2	1	1%	Hexyllaurate	23%	Poly(7)ethylene-glycol glyceryl-cocoate**C	26%	Polyoxyethylene-10-oleyl ether **A	20%	29.7%	anhydrous acetic acid	0.3%
3	2	10%	Hexyllaurate	10%	Poly(7)ethylene-glycol glyceryl-cocoate**C	20%	Polyoxyethylene-10-oleyl ether **A	20%	38.5%	anhydrous acetic acid	1.5%
4	3	8.2%	2,6,10,15,19,23-Hexamethyl-tetracosane	20.5%	Dodecanol	6.5%	Polyoxyethylene-10-oleyl ether **A	20.5%	40.6%	lactic acid 90%	3.7%
5	3	8.2%	Isopropylmyristate	20.5%	Dodecanol	6.5%	Polyoxyethylene-10-oleyl ether **A	20.5%	40.6%	lactic acid 90%	3.7%
5	3	8.2%	Isopropylmyristate	20.5%	Tetradecanol	6.5%	Polyoxyethylene-10-oleyl ether **A	20.5%	34.6%	lactic acid 90%, Colla-derm 350**	3.7% 6%
7	4	8.3%	Isopropyl-laurate	20.5%	Dodecanol	6.5%	Polyoxyethylene-10-oley ether **B	20.5%	41.3%	lactic acid 90%	2.9%

Example	active ingredient *		Org.solvent		Co-emulsifier		Emulsifier		dist. water	Additional excipients	
	No.	%	a		b	%	c	%			%
8	5	8.3%	Isopropyl laurate	20.6%	Dodecanol	6.6%	Polyoxyethlyene-10-oleyl ether **B	20.6%	41.2%	lactic acid acid 90%	2.7%
9	1	1.0%	Isopropyl laurate	20.0%	Dodecanol	7.0%	Polyoxyethylene-10-oleyl ether **A	18.0%	53.7%	lactic acid acid 90%	0.3%
10	6	0.5%	2,6,10,15,19,23-Hexamethyl-tetracosane	21.0%	Dodecanol	6.5%	Polyoxyethylene-10-oleyl ether **B	21.0%	26.0%	Polyethyl-englycol 400	25.0%
11	7	0.2%	2,6,10,15,19,23-Hexamethyl-tetracosane	20.5%	Dodecanol	8.8%	Polyoxyethylene-10-oelyl ether **B	20.5%	50.0%		
12	8	0.1%	Isopropyl laurate	22.5%	Dodecanol	8.0%	Polyoxyethylene-10-oleyl ether **A	22.5%	46.9%		
13	3	8.2%	2,6,10,15,19,23-Hexamethyl-teracosane	20.5%	Dodecanol	6.5%	Polyoxyethylene-10-oleyl ether **B	20.5%	41.0%	lactic acid 90%	3.3%
14	3	8.2%	Isopropyl laurate	20.5%	Dodecanol	6.5%	Polyoxyethylene-10-oleyl ether **B	20.5%	41.0%	lactic acid 90%	3.3%

Example	active ingredient *		Org. solvent		Co-emulsifier		Emulsifier		dist. water	Additional excipients	
	No.	%	a		b	%	c	%			%
15	3	8.2%	Lauryllactate	20.5%	Tetradecanol	6.5%	Polyoxyethylene-10-oleyl ether **B or A	20.5%	41.0%	lactic acid 90%	3.3%
16	3	8.2%	Myristyllactate	20.5%	Tetradecanol	8.0%	Polyoxyethylene-10-oleyl ether **A	20.5%	39.5%	lactic acid 90%	3.3%
17	4	8.3%	Isopropyl laurate	20.5%	Dodecanol	6.5%	Polyoxyethylene-10-oleyl ether **B	20.5%	41.3%	lactic acid 90%	2.9%
18	5	8.3%	Isopropyl laurate	20.6%	Dodecanol	6.6.%	Polyoxyethylene-10-oleyl ether **B	20.6%	41.2%	lactic acid 90%	2.7%
19	2	10%	Isopropyl myristate	20.5%	Propylene-glycol mono laurate	10%	Polyoxyethylene-10-oleyl ether **B	20.5%	35.6%	lactic acid 90%	3.4%
20	3	8.2%	Polyethyleneglycolglyceryl-fatty acid ester **D	20.5%	Dodecanol	6.5%	Polyoxyethylene-10-oleyl ether **B	20.5%	41.0%	lactic acid 90%	3.3%
21	9	4.0%	Hexyllaurate	13.0%	Poly(7)ethylene-glycol-glycerylcocoate **C	26.0%	Polyoxyethylene-10-oleyl ether **A	10.0%	16.0%	Propylen-glycol Isopropanol	6.0% 25.0%

Example	active ingredient		Org. solvent		Co-emulsifier		Emulsifier		dist. water	Additional excipients %	
	No.	%	a		c	%	c	%			%
22	2	10%	Propylene glycol mono-laurate	13%	Poly(7)ethylene-glycol-glycerylcocoate **C	26%	Polyoxyethylene-10-oleyl ether **A	20%	31%		
23	2	10%	Propylene glycol mono-laurate	13%	Poly(7)ethylene-glycol-glycerylcocoate **C	26%	Polyoxyethylene-10-oleyl ether **A	20%	16%	Alcohol (96%)	15%
24	3	8.2%	Isopropyl myristate	20.5%	Dodecanol	8%	Polyoxyethylene-10-oleyl ether **A	20.5%	39.1%	lactic acid 90%	3.7%
25	3	8.2%	2,6,10,15,19,23-hexamethyltetracosane	20.5%	Dodecanol	6.5%	Polyoxyethylene-10-oleyl ether **A	20.5%	41%	lactic acid 90%	3.3%

* Table of pharmacologically active agents

1. (E)-N-methyl-N-(1-naphthylmethyl)-3-phenyl-propen-2-ylamine.
2. (+)-1-methyl-2-[2-(α-methyl-p-chlorodiphenyl-methoxy)-ethyl]-pyrrolidine.
3. 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole.
4. 4-(1-methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-10(9H)-one.
5. 4-(1-methyl-4-piperidylidene)-9,10-dihydro-4H-benzo-(4,5)-cyclohepta-(1,2-b)-thiophene.
6. Griseofulvin.
7. Fluocinolone acetonide.
8. Triamcinolone acetonide.
9. 14-O-[5-(2-amino-1,3,4-triazolyl)thioacetyl]-dihydromutiline, also known as 14-[5-amino-4H-1,2,4-triazol-3-yl)-thioacetoxy]-14-deoxy-19,20-dihydromutilin.

**Table of commercial products

A BRIJ 97 HLB value 12.4 (ATLAS)
B VOLPO 10 HLB Value 12.4 (CRODA)
C CETIOL HE (HENKEL)
D LAFABRIL 1944S (GATTEFOSSE)

Colladerm 350: A solution of a Zn salt of a highly purified cosmetic polypeptide of collagen (STEPHAN CHEMICAL COMPANY).

Claims:

1. A skin penetration pharmaceutical composition incorporating a skin-penetrable pharmacologically active agent, wherein the composition is in the form of a microemulsion formed from skin compatible excipients.

2. A composition as claimed in claim 1 wherein the composition is in the form of a microgel.

3. A composition as claimed in claim 1 wherein the active agent is a difficultly skin-penetrable active agent.

4. A composition as claimed in claim 3 comprising from 5 to 30% by weight of a water-immiscible skin compatible solvent.

5. A composition as claimed in claim 1, 2 or 3 containing from 4 to 30% by weight of a skin compatible emulsifier.

6. A composition as claimed in claim 1, 2 or 3 comprising 10 to 30% by weight of a skin compatible coemulsifier.

7. A composition as claimed in claim 1, 2 or 3 comprising 15 to 55% by weight of water.

8. A composition as claimed in claim 1 containing 0.01 to 15% by weight of skin-penetrable pharmacologically active agent.

9. A composition as claimed in claim 8 containing from 5 to 15% by weight of skin-penetrable pharmacologically active agent.

10. A composition as claimed in claim 1 containing a skin compatible ester of an aliphatic (C_{3-18}) alcohol with an aliphatic (C_{10-22}) carboxylic acid.

11. A composition as claimed in claim 10 wherein the ester is chosen from isopropyl laurate, hexyl laurate, decyl laurate, isopropyl myristate and lauryl myristate.

12. A composition as claimed in claim 10 wherein the ester is isopropyl laurate, hexyl laurate or isopropyl myristate.

13. A composition as claimed in claim 10 wherein the ester is hexyl laurate.

14. A composition as claimed in claim 1 containing a skin

compatible hydrocarbon having a straight carbon (C_{12-32}) chain substituted by from 6 to 16 methyl groups and having up to 6 double bonds.

15. A composition as claimed in claim 14 containing squalane.

16. A composition as claimed in claim 1 containing a skin compatible mono-ester of ethylene glycol or propylene glycol with an aliphatic (C_{6-22}) carboxylic acid.

17. A composition as claimed in claim 16 wherein the ester is propylene glycol monolaurate or propylene glycol monomyristate.

18. A composition as claimed in claim 1 wherein the ester is a skin compatible ester of an aliphatic (C_{12-22}) alcohol with lactic acid.

19. A composition as claimed in claim 18 wherein the ester is myristyl lactate or lauryl lactate.

20. A composition as claimed in claim 1 containing a skin compatible aliphatic (C_{12-22}) alcohol.

21. A composition as claimed in claim 20 wherein the alcohol is dodecanol, tetradecanol, oleyl alcohol, 2-hexyldecanol or 2-octyldecanol.

22. A composition as claimed in claim 20 wherein the alcohol is dodecanol.

23. A composition as claimed in claim 1, ~~2 or 3~~ containing a skin compatible ester of a poly(2-7)ethylene glycol glycerol ether having at least one free hydroxyl group and an aliphatic (C_{6-22}) carboxylic acid.

24. A composition as claimed in claim 23 wherein the ester is poly(7)ethylene glycol glyceryl cocoate.

25. A composition as claimed in claim 1, 2 or 3 containing a skin compatible mono or diester of glycerol with an aliphatic (C_{6-22}) carboxylic acid.

26. A composition as claimed in claim 1, 2 or 3 containing a skin compatible ester having at least one hydroxyl group of a poly(2-10)glycerol with an aliphatic (C_{6-22})carboxylic acid.

27. A composition as claimed in claim 1 containing a skin compatible mono-ether of a polyethyleneglycol with an aliphatic (C_{12-18}) alcohol having an HLB value of from 10 to 18.

28. A composition as claimed in claim 27 wherein the mono ether is polyoxyethylene(10)oleyl ether.

29. A composition as claimed in claim 1, 2 or 3 containing a skin compatible ester of an aliphatic (C_{6-22}) carboxylic acid with

a) a polyethylene glycol

b) a saccharose

c) a sorbitan or

d) a polyethylene glycol sorbitan ether,

the ester having an HLB value of from 10 to 18.

30. A composition according to claim 1, ~~2 or 3~~ containing as active agent (E)-N-methyl-6,6-dimethyl-N-(naphthyl-methyl)hept-2-en-4-inyl-1-amine, naftifin, ketotifen, pizotifen, griseofulvin, fluocinolone acetonide, triamcinolone acetonide, 14-O-[5-(2-amino-1,3,4-triazolyl) thioacetyl]-dihydro-mutiline, or proquazone.

31. A composition according to claim 1, containing as active agent clemastine.

32. A composition according to claim 1, containing as active agent tizanidine.

33. A composition according to claim 30 containing 14-O-[5-(2-amino-1,3,4-triazolyl)thioacetyl]-dihydro-mutiline.

34. A composition according to claim 31 or 33 containing hexyl laurate, poly(7)ethylene glycol glyceryl cocoate and polyoxyethylene(10)oleylether.

35. A composition according to claim 32 containing
6 to 10% of tizanidine,
15 to 25% of water-immiscible organic solvent,
15 to 25% of emulsifier,
5 to 10% of co-emulsifier, and
30 to 35% of water.

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36. A composition according to claim 35 containing isopropyl laurate, polyoxyethylene(lo)oleyl ether and dodecanol.

37. A process for the production of a skin-penetrable pharmaceutical composition which comprises forming a microemulsion from water and a skin-penetrable pharmacologically active agent and skin compatible excipients capable of functioning as a water-immiscible organic solvent, an emulsifier and a co-emulsifier.

38. A process according to claim 37 wherein the skin-penetrable pharmacologically active agent, water-immiscible organic solvent and emulsifier are heated to a maximum of 100°C to form an emulsion and then cooled to form a microemulsion.

39. A skin penetration pharmaceutical composition incorporating a skin-penetrable pharmaceutically active agent selected from (E)-N-methyl-6,6-dimethyl-N-(naphthylmethyl)hept-2-en-4-inyl-1-amine, naftifin, ketotifen, pizotifen, griseofulvin, fluocinolane acetonide, triamcinolone acetonide, 14-O-[5-(2-amino-1,3,4-triazolyl) thioacetyl]-dihydro-mutiline, or proquazone, wherein the composition is in the form of a microemulsion formed from skin compatible excipients.

40. A skin penetration pharmaceutical composition incorporating a skin-penetrable pharmaceutically active agent selected from clemastine and tizanidine, wherein the composition is in the form of a microemulsion formed from skin compatible excipients.

41. A topical skin penetration pharmaceutical composition incorporating tizanidine, wherein the composition is in the form of a microemulsion formed from skin compatible excipients.

42. A semi-solid skin penetration pharmaceutical composition incorporating tizanidine, wherein the composition is in the form of a microemulsion formed from skin compatible excipients.

43 A topical skin penetration pharmaceutical composition comprising tizanidine together with a skin compatible diluent or carrier.

SUBSTITUTE

REMPLACEMENT

there are NO DRAWINGS

il n'y a PAS DE DESSINS